II. REMARKS

Claims 1-29 are pending in the subject application. Claims 24 to 28 are withdrawn from consideration as a result of a requirement for restriction. Claims 1 to 23 and 29 stand rejected.

The specification has been amended in response to the Notice to Comply. Claim 1 has been amended without prejudice or disclaimer. The amendments to the specification and claim 5 are not related to patentability and are not substantive. They were made to conform the specification and claims as required by the rules of 37 C.F.R.. Accordingly, an issue of new matter is not raised by these amendments and entry thereof is respectfully requested. Amended claims 1 to 23 and 29 are currently under examination.

Attached hereto is a marked-up version of the changes made to the specification and claims. The attached page is captioned "Version with markings to show changes made".

In view of the preceding amendments and remarks that follow, withdrawal of the Notice to Comply, objections and rejections of the application are respectfully requested.

Applicant's undersigned attorney would like to thank Examiner Nguyen for the courtesy of the telephonic interview. The interview was helpful to a complete understanding of the issues set forth in the outstanding Office Action.

Sequence Requirements Under 37 C.F.R. § 1.821

The specification stands was objected to on the ground that it did not conform to the requirements of 37 C.F.R. § 1.821. Enclosed with this reply is a paper copy of the sequence listing and a computer diskette containing an electronic copy of the same. Applicant's undersigned attorney hereby states that the paper and electronic copies of the sequence listing are identical. Accordingly, in view of these submissions, reconsideration and withdrawal of the objection to the specification is respectfully requested.

35 U.S.C. § 102

Claims 16-23 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by either Needham (U.S. Pat. No. 5,882,679) or Abra (U.S. Pat. No 6,126,966). The Office alleged that

the claims embrace a product by process, namely an encapsulated cisplatin obtainable by the method of claims 11 or 13, and conventional tumor treatment method of administering intravenously the encapsulated cisplatin. Needham is alleged to teach the same on columns 4, 5, 11-12, 18 (lines 35-67) 38, and 39 and Abra et al. is alleged to teach the same throughout the patent disclosure (column 4, column 13 or 14).

The Office opined that therefore, absent evidence to the contrary, the encapsulated cisplatin produced by the method of Needham or Abra is the same that of the claims.

Applicant respectfully traverses. Claims 16 to 23 are directed to encapsulated cisplatin-containing micelles for therapy. The micelles are made by combining a suitable buffer solution, cisplatin and a negatively charged phosphatidyl glycerol lipid derivative in a molar ratio of 1:1 to 1:2 to form a cisplatin mixture. The mixture is then combined with an effective amount of at least a 30% ethanol solution to form a cisplatin mixture in its aqua form in micelles. In another embodiment, the micelles are produced by combining a suitable buffer solution, cisplatin and an effective amount of at least a 30% ethanol solution to form a cisplatin/ethanol solution. The solution is then combined with a negatively charged phosphatidyl glycerol lipid derivative in a molar ratio of 1:1 to 1:2 to form cisplatin in its aqua form in micelles.

Accordingly, the micelles are composed in part of cisplatin in its aqua form and a phosphatidyl glycerol lipid as the polymer that forms the micelle.

Needham discloses liposome micelles that in one aspect, may contain insoluble drugs such as cisplatin.

> "Micelles can solubilize otherwise insoluble organic material by incorporating it within a hydrophobic interior. In the present active agent delivery system, the central region of a micelle can dissolve otherwise totally water-insoluble active agents. The micelle is made by aggregating the active agent with a lipid surfactant such as a lysolipid. Additionally, a cosolvent may be utilized converting the simple micelle into a micro-emulsion or emulsion where the central core is made up not just the lipid chains but also a second oily component along with the active agent." (col. 11, lines 56-64 of Needham).

In a separate embodiment, "a hydrophobic acyl chain is attached to the active agent to allow the drug to be anchored into the micelle." (See col. 12, lines 3 to 8). The micelles are then encapsulated into liposomes.

Needham fails to teach the subject invention for several reasons. First, the Needham patent uses a zwitterionic lipid, MOPC, for the micelle, not a phosphatidyl glycerol lipid as required by the claims. Phosphatidyl glycerol lipids are aniomic.

Second, Needham does not create a micelle containing an aqeuos form of an insoluble drug in a negatively chagred lipid. Needham uses the water solubility of the drug for micellar association from the outside of the micellar structure to the inside (Fig 18). In contrast, the claimed micelles are a defined molecular structure with the cisplatin in the inside. In one embodiment, Needham solubilizes into the hydrophobic part of the micelle insoluble organic material (e.g., TAXOL) by use of cosolvents. Cosolvents are proposed by Needham to convert micelles into emulsions. Applicant's micelles are not emulsions nor do they use co-solvents. In a separate embodiment, Needham attaches a hydrophobic acyl chain to TAXOL (column 12) to "solubilize" the drug. In fact, he is attaching the drug to the micelle, not maintaining it in any solubilzed form, aqueos or non-aqueos. In sum, the micelles disclosed by Needham have the drug on the outside of the micelle if electrostatic forces are being evoked or in the aliphatic chains of the molecule which can never be the case for cisplatin. Thus, Needham does not teach the invention of the rejected claims.

Abra does not teach aqueous cisplatin in micelles. As the Office admitted on page 4 of the Office Action ("Abra et al. do not teach incorporations of micelles contained in the liposomes. . . ."). Rather, Abra teaches encapsulation or capture of the drug in a lipid bilayer. A micelle-like structure is not described. Abra also does not rely on electrostatic interaction between the drug and the negatively charged lipid derivative to form a micelle and cisplatin is not in an aqueous form.

For these reasons, the rejections under 35 U.S.C. § 102 are in error and should be removed.

35 U.S.C. § 103

Claims 1-4 and 7-21, 23 and 28 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Abra (U.S. Pat. No. 6,126,966) taken with Needham (U.S. Pat. No. 5,882,679) and Shaw (U.S. Pat. No. 6,001,817).

Abra is alleged to teach that a liposomal composition containing an entrapped cisplatin compound which is composed of a vesicle-forming lipid, *e.g.*, DSPE (distearyl phosphatidyl glycerol) derivatized with a hydrophillc polymer (PEG which has been derivatized via a linking agent which is itself negatively charged, see Figure 3) and/or cholesterol, and/or HSPC is effective for use to increase the stability of cisplatin during its *in vivo* delivery via intravenous route to a tumor site (claim 1, columns 5 through 6, columns 9-12, column 14). Column 2, third paragraph, of Abra is alleged to specifically disclose that cisplatin is entrapped in the liposomes at a drug-to-lipid ratio of between about 10 to 20 μg/mg total lipid. Column 9, 7th paragraph of Abra allegedly discloses that 50-200 mg/mi of total lipids (MW: 2748 for DSPE-PEG 2000 or 2772 for DSPG-PEG -2000) is mixed with 8.5 mg/cisplatin (MW: 300) containing buffered solution and that column 9 bridging column 10 discloses the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form encapsulated cisplatin. The Office admitted that Abra does not teach incorporations of micelles contained in the liposomes so as to increase the stability of the encapsulated cisplatin/liposomes and the retention of cisplatin, wherein the micelles are associated with cisplatin by ionic interactions).

However, the Office opined that, Needham provides a solution to the problem of insolubility of cisplatin that affects that activity of cisplatin and the integrity of the liposomal bilayes (column 4 bridging column 5, column 38, lines 38-67, by mainly incorporating a micellar structure coupled with polymers (PEG which Is hydrogen acceptor) and/or cholesterol (column 22) within any conventional liposomal structure including phosphatidyl glycerol (column 8, line 52) so as to increase the solubility and retention of active agents or molecules that are insoluble (column 11 through column 12). Needham also is alleged to teach at Column 12, second end third paragraphs, and column 12 bridging column 13, that ionic micelles can be formulated by

active agents with charges opposite to that designed into the micelles and that column 18 discloses that active agent containing micelles can be routinely made by the prior art and that the micelles can be suspended in a buffer such as water or saline solution.

The Office alleged that Shaw teaches that buffered solution containing additional excipients including at least 30% ethanol can be used to reconstitute cisplatin in a pharmaceutical composition.

The Office opined that therefore, it would have been obvious for one of ordinary skill in the art to have incorporated micellar structure coupled with polymers and cholesterol within the liposomal structure so as to increase the solubility and retention of active agents or molecules that are insoluble (column 11 through column 12), wherein the micellar structure is associated to cisplatin by ionic interactions. One would have been motivated to do so because Needham provides a solution to the problem of insolubility of cisplatin that affects that activity of cisplatin and the integrity of the liposomal bilayers by mainly incorporating a micellar structure coupled with polymers and/or cholesterol within the liposomal structure so as to increase the solubility, retention, and activity of active agents or molecules that are insoluble.

The Office opined that it would also have been obvious for one of ordinary skill in the art to have employed the step of reconstituting cisplatin in at least a 30% ethanol solution. One would have been motivated to do so because Abra on column 9 bridging column 10 discloses the step of mixing a lipid/cisplatin mixture with an ethanol solution to form encapsulated cisplatin, and/or because Shaw teaches that buffered solution containing additional excipients including at least 30% ethanol is used to reconstitute cisplatin in a pharmaceutical composition.

It also is alleged that it would have been obvious for one of ordinary skill in the art to have further employed a suitable lipid, *e.g.*, cholesterol, DSPE and/or HSPC, and a hydrophilic polymer as stabilizer complexes to enhance the stability of the liposome taught by the combined cited references. One of ordinary skill in the art would have been motivated to have employed the stabilizer complexes in the liposomes of the combined cited references because both Abra and Needham teach that a liposomal composition containing an entrapped cisplatin compound which is composed of a vesicle-forming lipid derivatized with a hydrophilic polymer (PEG),

and/or cholesterol, and/or HSPC is effective for use to increase the stability of cisplatin during its *in vivo* delivery to a tumor site (claim 1, columns 5 through 6, columns 9-12).

Applicant respectfully traverses.

First, Applicant incorporates by reference the remarks set forth in reply to the rejection under 35 U.S.C. § 102. The micellular portion of the encapsulated liposome is not taught by Needham or Abra. Needham does not teach one to convert cisplatin to its aqua form and then rely on electrostatic interactions between the drug and micelle to encapsulate the drug. Abra does not teach cisplatin in its aqua form, nor does it teach or suggest a micelle for encapsulation of cispatin. Rather, Abra teaches the conventional lipid bilayer to encapsulate cisplatin.

Shaw teaches pharmaceutical delivery of cisplatin by combining the drug with an amino acid such as guanine. Accordingly, there is no teaching or suggestion in Shaw that ethanol can be used in the production of cisplatin-encapsulated micelles. In addition, Shaw is directed to a completely different field of endevour or "art" and therefore is not a valid reference under 35 U.S.C. § 103.

The combination of the references fail to teach or suggest the invention of the claims because none teach or suggest micelle encapsulated cisplatin, wherein the cisplatin is in the aqua form and the combination lacks the motivation to combine the references in the manner the Office has to allegedly arrive at the invention of the claims. Each of the cited references teach a different solution to the problem of insolubility of cisplatin. Abra uses conventional liposomes, but the cisplatin is not in aqua form. Needham teaches that many drugs can be encapsulated, one of which is cisplatin, by use of totally different technique which results in a product having different elements that the invention of the claims. Needham uses a cosolvent or an acyl chain. Needham does not teach that any of the insoluble can agents be converted to an ionic form and then combined with negatively charged phosphatidyl glycerol. Needham also does not teach or suggest phoshatidyl glycerol as a possible micellular component which can be combined with pre-made liposomes, for example. The references also do not teach how to make the micelle and liposome structure of Applicant's claims. Accordingly, there is no suggestion in the references to combine Needham and Abra in the manner suggested by the Office and one of skill in the art

would not be lead to pick and choose among the hundreds of variations proposed by Needham. At best, Needham and/or Abra teach *away* by suggesting different solutions to the problem solved by Applicant.

Shaw fails to shore up the deficiencies of Needham and Abra. Moreover, because Shaw is directed to a different technical field, there is no motivation to combine Shaw with Abra and/or Needham.

The rejection of the claims as allegedly obvious over Needham, Abra and Shaw is in error and should be removed.

Claims 9, 13, 16, 17 and 19-21 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Abra taken with Needham and Shaw, and further in view of Unger (U.S. Pat. No. 6,028,066).

The Office stated that the combined cited references of Abra, Needham and Shaw teach the encapsulation method of claim 9 as indicated above.

To the extent that the combined cited references do not teach explicitly the use of hyaluronic acid - DSPE in the method, the Office argued that it would have been obvious for one of ordinary skilled in the art to have incorporated any glycosaminoglycan including hyaluronic acid in any of the lipid stabilizer complex taught by the combined cited references, particularly glycosaminoglycan is routinely employed in the prior art to increase the stabilization and antithrombic properties of the lipid complexes. One of ordinary skill in the art would have been motivated to have employed including hyaluronic acid in any of the lipid stabilizer complex taught by the combined cited references because of the reasons set forth in the immediately preceding sentence and because Unger teach that lipid complexed with hyaluronic acid can be used a stabilizer in any liposomal delivery composition (column 23, last paragraph).

Claims 1, 2 and 5 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Abra taken with Needham and Shaw, and further in view of Lee (U.S. Pat. No. 5,908,777).

The Office stated that the combined cited references of Abra, Needham and Shaw teach the encapsulation method of claims 1 and 2 as indicated above. To the extent that the combined

cited references do not teach explicitly the use of a fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution entrapped in the liposomal composition, Lee teach that a lipidic complex containing a fusogenic peptide enhances the fusion and delivery of the lipid complex through cell membrane of a target cell (column 7 citing Haensler and Szoka), and that fusogenic peptide can be derivatized by adding a string of negatively-charged amino acids (glutamic acid residues) at the N or C-terminus of the peptide so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution (column 7).

The Office alleged that it would have been obvious for one of ordinary skill in the art to have further employed a fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution. The Office argued that one of ordinary skill in the art would have been motivated incorporate a fusogenic peptide fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus as a ionic complex with the cisplatin/lipid micelles of the combined cited references because Lee teaches that a lipidic complex containing a fusogenic peptide enhances the fusion and delivery of the lipid complex through cell membrane of a target cell (column 7 citing Haensler and Szoka), and that fusogenic peptide can be derivatized by adding a string of negatively-charged amino acids (glutamic acid residues) at the N or C-terminus of the peptide so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution.

Claims 1, 2, 5 and 6 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Abra, Needham and Shaw, and further in view of Lee (U.S. Pat. No. 5,908,777) and Gebeyehu (U.S. Pat. No. 5,334,761).

The Office further rejected claims 1, 2 and 5 as allegedly unpatentable over Abra, Needham and Shaw, and further in view of Lee is applied here as indicated above. The Office stated that to the extent that the combined cited references do not teach the use of a cationic lipid/DOPE complex as an additional fusogenic substance so as to enhance the transport of the

cisplatin/lipid complex of the combined cited references, Gebeyehu is one of many exemplified references that teach that cationic lipid/DOPE complex due to its enhanced affinity to cell membrane are routinely employed in the prior art to enhance the delivery of bioective compounds across the cell membrane of a target cell (entire document, abstract, column 1, column 4).

The Office opined that it would have been obvious for one of ordinary skill in the art to have further employed any suitable cationic lipid/DOPE complex in the combined cisplatin/lipid/fusogenic peptide complex as taught by combined cited references and that one of ordinary skill in the art would have been motivated to have added any suitable cationic lipid/DOPE complex in the combined cisplatin/lipid/fusogenic peptide complex because Gebeyehu is one of many exemplified references that teach that cationic lipid/DOPE complex due to its enhanced affinity to cell membrane are routinely employed in the prior art to enhance the delivery of bioactive compounds across the cell membrane of a target cell (entire document, abstract, column 1, column 4), and because one would have expected that the addition of a fusogenic cationic lipid/DOPE complex would further generate an additive fusogenic effect so as to enhance the delivery of the cisplatin compound to target tumor cells.

Applicant respectfully traverses all of the above noted rejections for the reasons set forth in reply to the rejection over the combination Needham, Abra and Shaw. The primary references fail to teach or suggest the micelle structure, the micelle encapsulated in a liposome, nor how to make them for the reasons cited above. The newly applied references fail to shore of the deficiencies present in the primary references. Applicants respectfully request that these grounds for rejection of the claims under 35 U.S.C. § 103 be withdrawn.

35 U.S.C. § 112 Second Paragraph

Clams 1-23, and 29 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for falling to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Base claim 1 and claims dependent therefrom are allegedly indefinite on the ground that it is not apparent as to which of the three components is referred by the molar ratio of 1: 1 or 1: 2. The Office suggested that a change to "wherein the molar ratio between cisplatin and the lipid derivative is 1:1 to 1:2" is suggested.

Claim 1 (and therefore dependent claims, e.g., claim 5) has been amended as suggested by the Office. The amendment of claim 1 is made to more clearly point out the invention of the claims and does not effect the scope of the claims or equivalents thereof. In view of these amendments, removal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

III. CONCLUSION

No additional fee is deemed necessary in connection with the filing of this Amendment and Response. However, if the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-1189**, referencing no. **23896-7002**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Should a telephone advance prosecution of the subject application, the Examiner is invited to contact the undersigned at (650) 849-4950.

Respectfully submitted,

Date: June 28, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Page 22, lines 9 through 16 are amended as follows:

DOPE (dioleyl phosphatidyl ethanolamine) is a fusogenic lipid; elastase cleavage of N-methoxy-succinyl-Ala-Ala-Pro-Val-DOPE (SEQ ID NO:10) converted this derivative to DOPE (overal positive charge) to deliver an encapsulated fluorescent probe, calcein, into the cell cytoplasm (Pak et al., 1999). An oligodeoxynucleic sequence of 30 bases complementary to a region of beta-endorphin mRNA elicited a concentration-dependent inhibition of beta-endorphin production in cell culture after it was encapsulated within small unilamellar vesicles (50 nm) containing dipalmitoyl-DL-alpha-phosphatidyl-L-serine endowed with fusogenic properties (Fresta et al., 1998).

Additional fusogenic peptides (SEQ ID NOS:4 through 9) useful in the methods of this invention are described in Table 1, below.

Claims 1, 10, 15 to 22 and 28, are amended as follows:

1. (Twice Amended) A method for producing cisplatin micelles, comprising:

a) combining a suitable buffer solution, cisplatin with an effective amount of at least a 30% ethanol solution to form a cisplatin/ethanol solution; and

b) combining the solution with a negatively charged phosphatidyl glycerol lipid derivative wherein the molar ratio between cisplatin and the lipid derivative is 1:1 to 1:2 [in a molar ratio of 1:1 to 1:2], thereby producing a cisplatin mixture in its aqua form in micelles.

10. (Amended) The encapsulated cisplatin lipid micelle obtainable by the method of claim 9.

15. (Amended) The method of claim 14, wherein removal of the ethanol is by dialysis of the cisplatin micelles through permeable membranes to remove the ethanol.

16. (Twice Amended) An encapsulated cisplatin lipid micelle obtainable by the method of claim 11.

17. (Twice Amended) An encapsulated [cisplatin] cisplatin/lipid complex obtainable by the method of claim 13.

18. (Twice Amended) A method for delivering cisplatin to a cell comprising contacting the cell with the encapsulated cisplatin lipid micelle of claim 16.

19. (Amended) A method for delivering cisplatin to a cell comprising contacting the cell with the encapsulated [cisplatin] cisplatin/lipid complex of claim 17.

20. (Amended) A method for inhibiting the growth of a tumor in a subject, comprising administering to the subject an effective amount of the encapsulated cisplatin lipid micelle of claim 16.

21. (Amended) A method for inhibiting the growth of a tumor in a subject, comprising administering to the subject an effective amount of the encapsulated [cisplatin] cisplatin/lipid complex of claim 17.

22. (Twice Amended) A method for targeting solid tumors and metastases in a subject comprising intravenous administration of an effective amount of the encapsulated cisplatin [of claims 16 or 17] micelle of claim 16 or the cisplatin/lipid complex of claim 17.

28. (Amended) A composition comprising the encapsulated cisplatin micelle of claim 10 and a drug selected from the group consisting of doxorubicin, fluorodeoxyuridine, bleomycin, adriamycin, vinblastin, prednisone, vincristine, taxol.